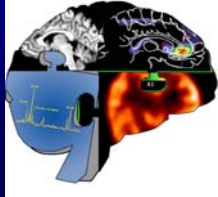


## Positron Emission Tomography: Tool to Facilitate Drug Development and to Study Pharmacokinetics



Robert B. Innis, MD, PhD  
Molecular Imaging Branch  
National Institute Mental Health

October 9, 2008

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### Outline of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling of plasma concentration and tissue uptake can measure receptor density
4. Study drug distribution: "peripheral" benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination

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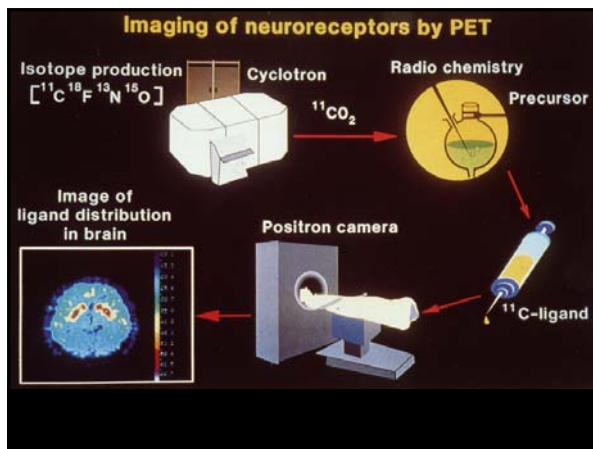
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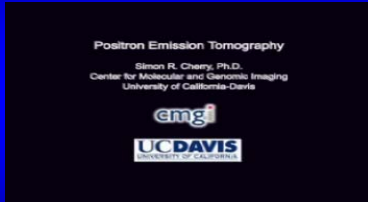
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## *Positron Emission Tomography*



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## PET vs. MRI

	PET	MRI
Spatial Resolution	2 – 6 mm	<< 1 mm
Sensitivity	$10^{-12}$ M	$10^{-4}$ M
Temporal Resolution	minutes	<1 sec

Radionuclide ( $^{11}\text{C}$ ): high sensitivity  
Ligand (raclopride): high selectivity  
Radioligand [ $^{11}\text{C}$ ]raclopride: high sensitivity & selectivity

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### **Radioligand = Drug + Radioactivity**

#### **1. Drug administered at tracer doses**

- a) No pharm effects
- b) Labels <1% receptors
- c) Labeled subset reflects entire population

#### **2. Radioligand disposed like all drugs**

- a) Metabolism & distribution

#### **3. Radiation exposure**

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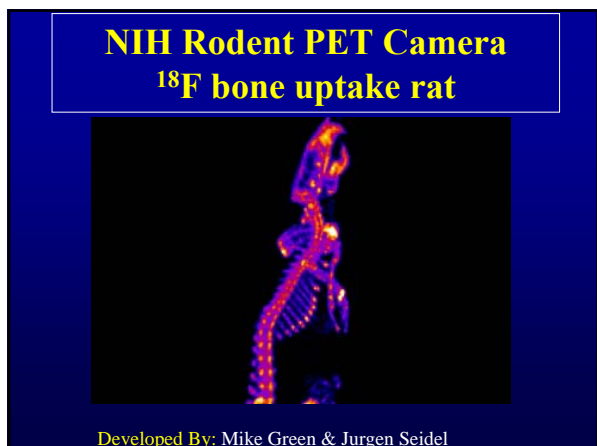
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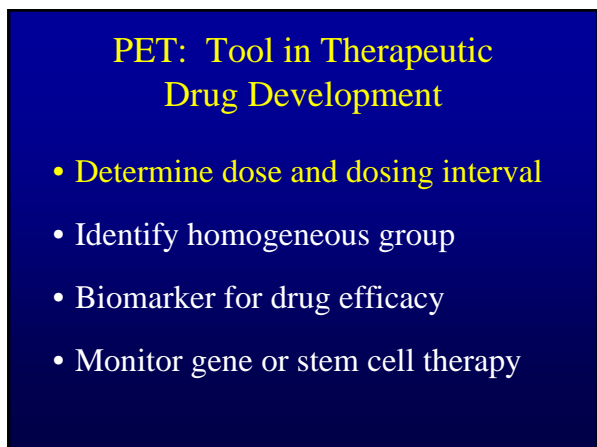
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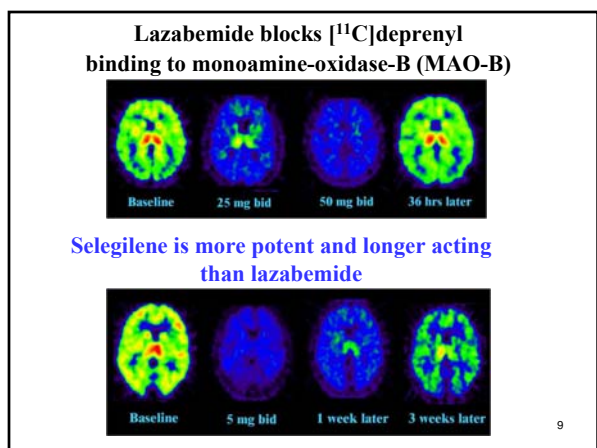
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## PET: Tool in Therapeutic Drug Development

- Determine dose and dosing interval
- Identify homogeneous group
- Biomarker for drug efficacy
- Monitor gene or stem cell therapy

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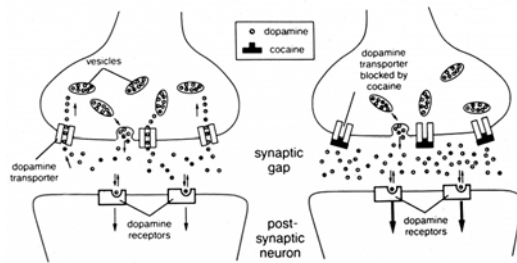
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### Dopamine Transporter: Located on DA Terminals Removes DA from Synapse



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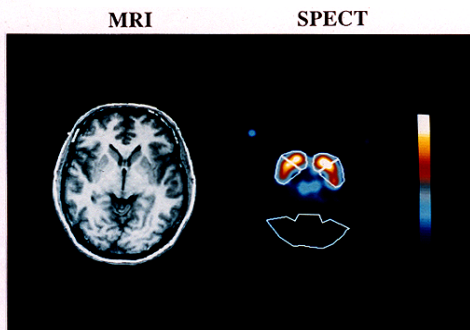
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### SPECT Imaging of Dopamine Transporter in Caudate and Putamen of Human Brain



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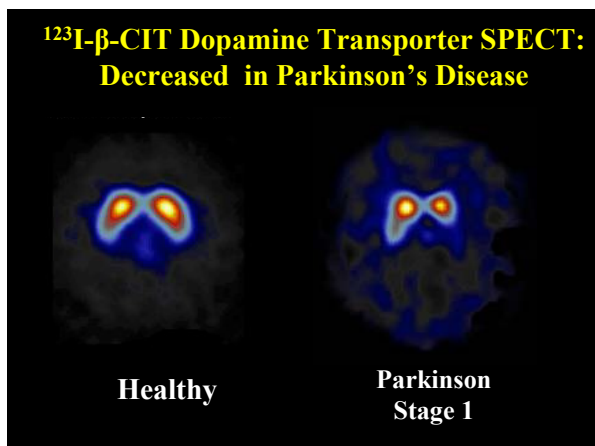
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**PET: Tool in Therapeutic  
Drug Development**

- Determine dose and dosing interval
- Identify homogeneous group
- **Biomarker for drug efficacy**
- Monitor gene or stem cell therapy

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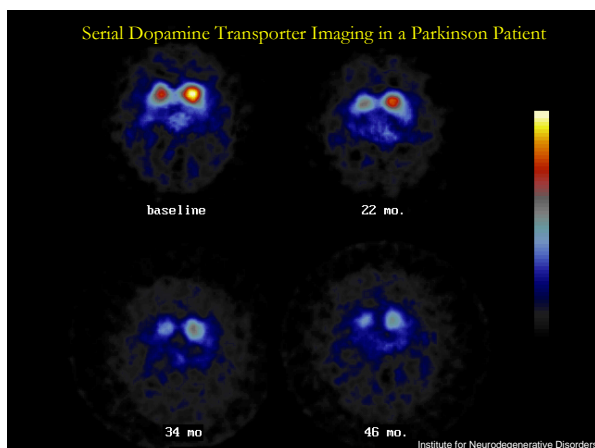
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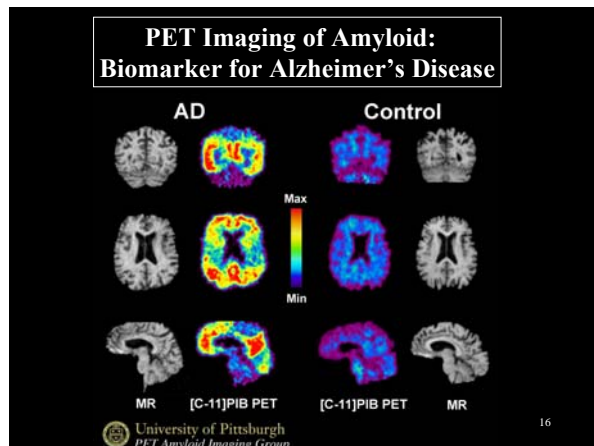
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**PET: Tool in Therapeutic Drug Development**

- Determine dose and dosing interval
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- Monitor gene or stem cell therapy

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**Gene Therapy Using Viral Vectors**

Viral vectors deliver gene that synthesizes dopamine (DA)

Infuse virus into striatum (target cells)

**Target cells express the DA gene**

The diagram illustrates the process of gene therapy. It starts with a DNA (Gene) being encapsulated in an AAV (Adeno-Associated Virus). The AAV is then released into a patient cell. Once inside the cell, the gene is expressed, leading to the production of a therapeutic protein. The diagram also shows a syringe infusing the virus into the striatum of a patient.

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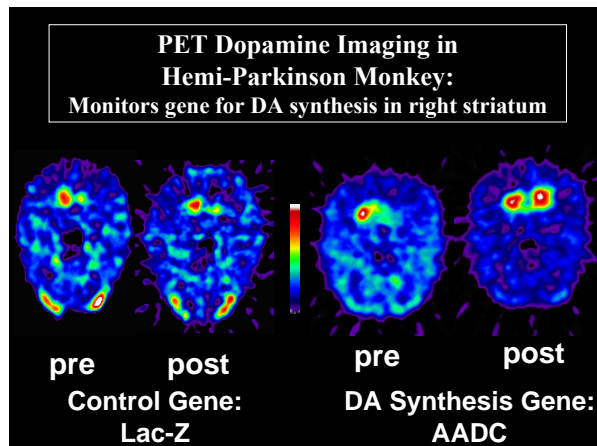
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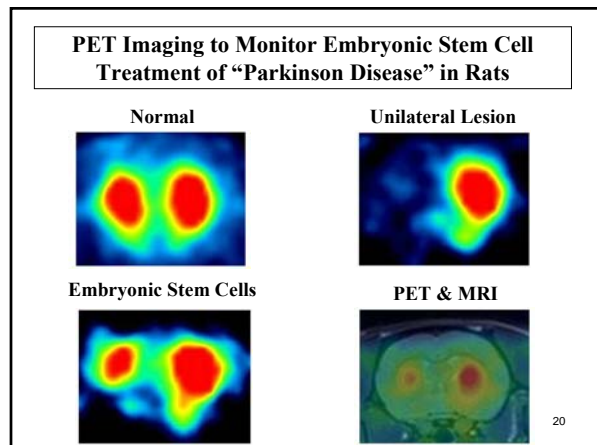
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**Outline of Talk**

1. PET has high sensitivity and specificity
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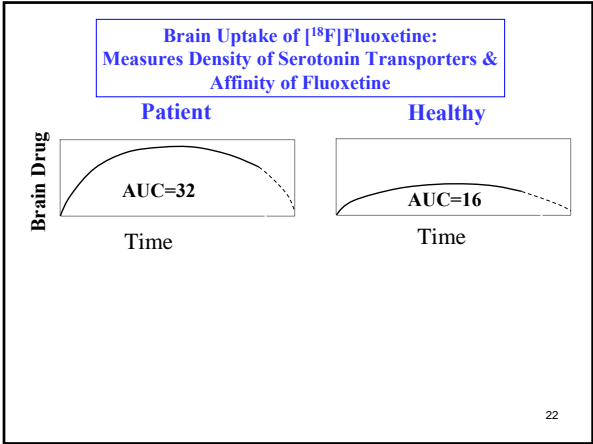
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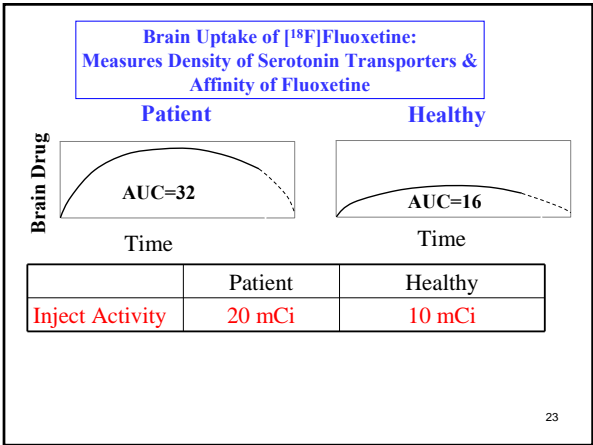
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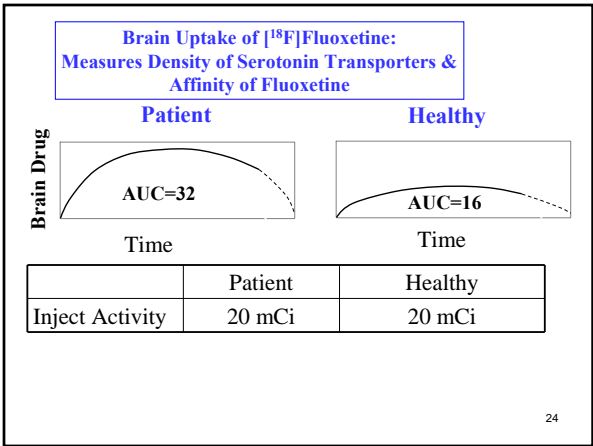
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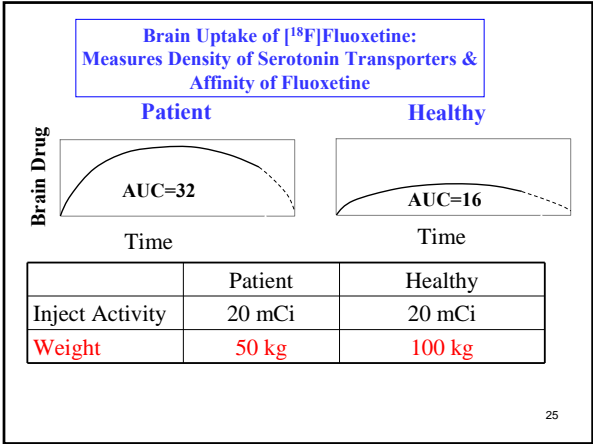
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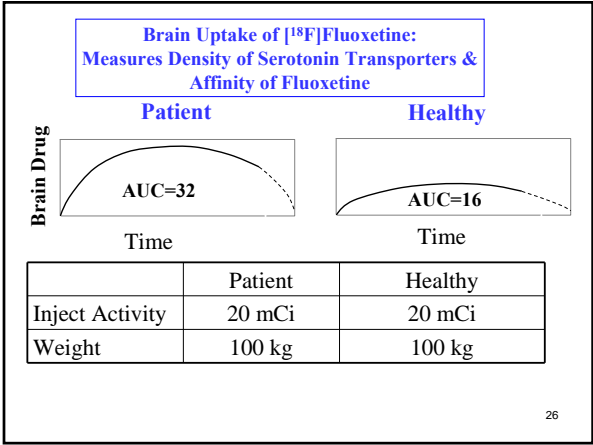
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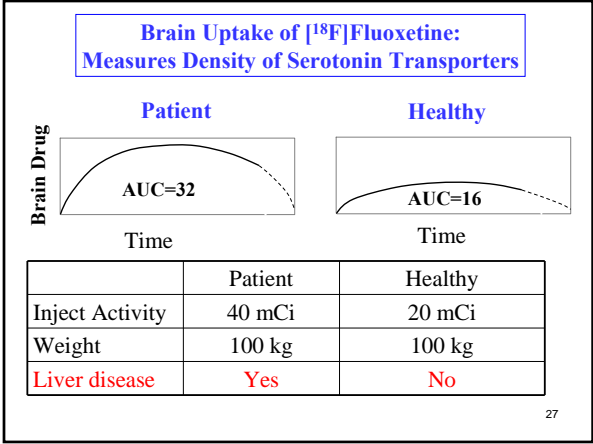
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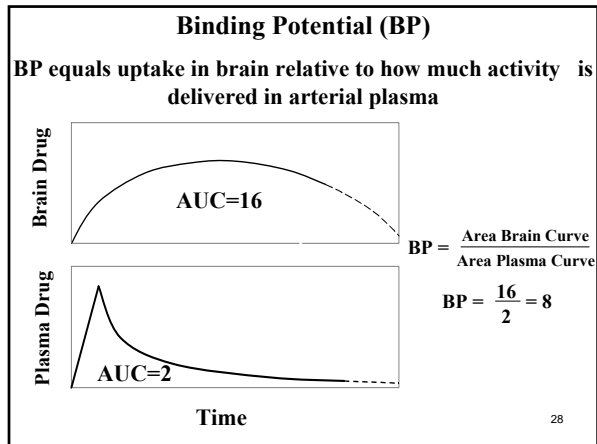
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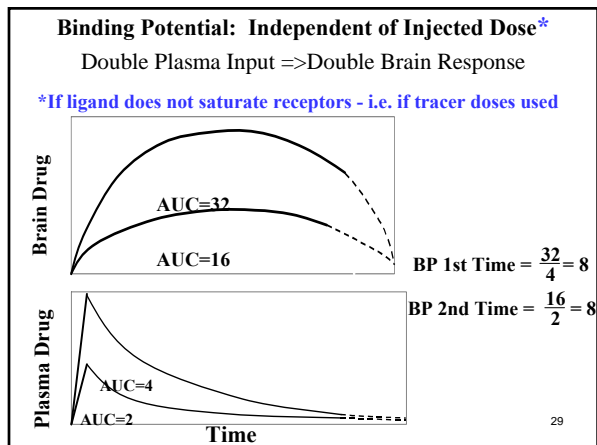
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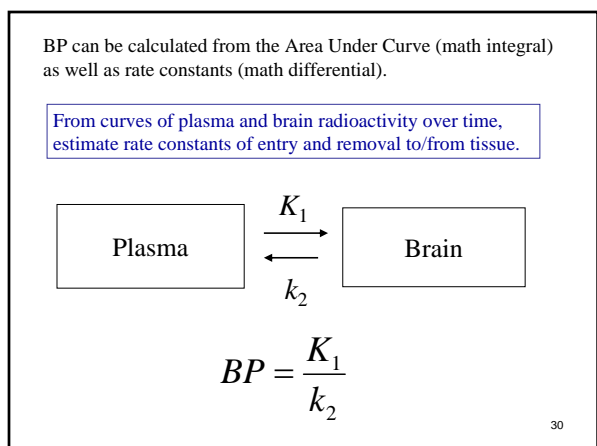
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**Tissue uptake is proportional to density of receptors and the affinity of the drug**

**Binding Potential**  $BP = \frac{B_{\max}}{K_D} = B_{\max} \times \frac{1}{K_D} = B_{\max} \times \text{affinity}$

$B_{\max}$  = receptor density

$K_D$  = dissociation binding constant

$\frac{1}{K_D}$  = binding affinity drug

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**SUMMARY PET KINETICS**

- Organ uptake is proportional to receptor density and affinity of drug
- Binding Potential (BP) = density X affinity
- "Drug Exposure" to tissue is AUC of:  
plasma concentration vs. time
- "Response" (uptake) of tissue is AUC of:  
tissue concentration vs. time

$$BP = \frac{\text{Response}}{\text{Exposure}} = \frac{AUC_{\text{tissue}}}{AUC_{\text{plasma}}}$$

- BP also equals ratio of rate constants of entry and removal to/from tissue

$$BP = \frac{K_1}{k_2}$$

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**Major Point of PET Pharmacokinetics  
(in words)**

- Plasma pharmacokinetics provides a limited view of what's happening to drug in plasma.
- PET provides a limited view of what's happening to drug in tissue.
- **Concurrent measurement of drug in plasma and of drug in tissue allows quantitation of the target of drug action – i.e., receptor.**

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**Outline of Talk**

- 1. PET has high sensitivity and specificity
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**“Peripheral” Benzodiazepine Receptor**

- 1. Mitochondrial protein highly expressed in macrophages and activated microglia
- 2. Exists in periphery and brain
- 3. Multiple potential functions: steroid synthesis, nucleotide transport
- 4. Distinct from typical benzodiazepine GABA<sub>A</sub> receptor in brain
- 5. Marker for cellular inflammation

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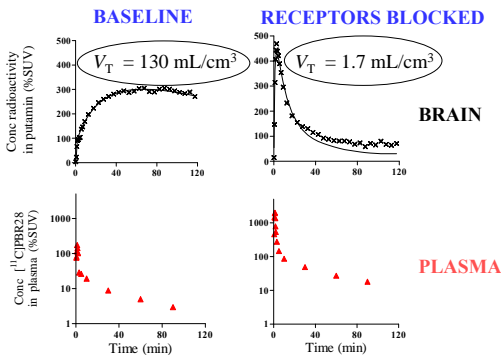
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**Receptor Blockade [<sup>11</sup>C]PBR28 in Monkey Brain: more radioligand in plasma and brain**



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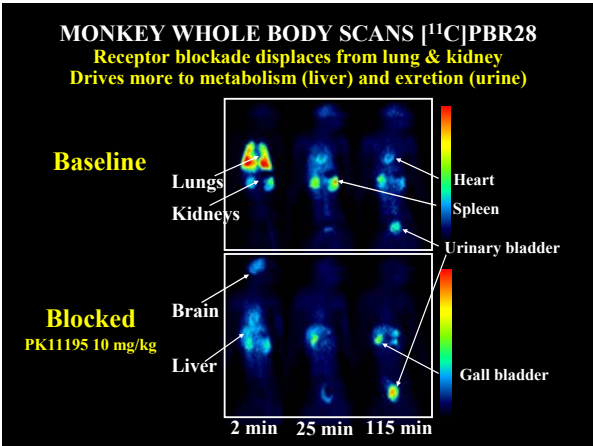
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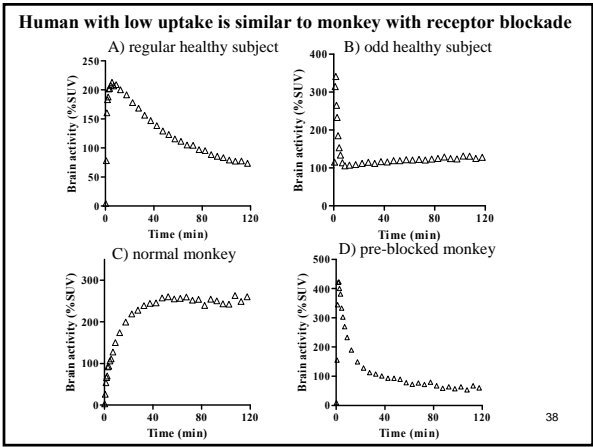
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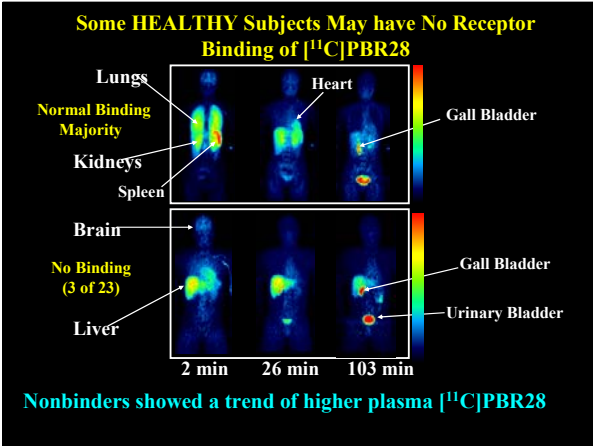
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## INFLAMMATION IMAGING On-going Studies

Neurocysticercosis

Multiple sclerosis

HIV with cognitive impairment

Alzheimer's disease

Atherosclerosis

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## Outline of Talk

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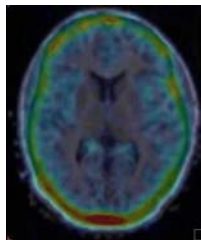
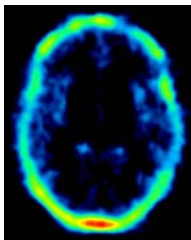
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[<sup>18</sup>F]FCWAY: Defluorination  
Bone uptake: human skull at 2 h



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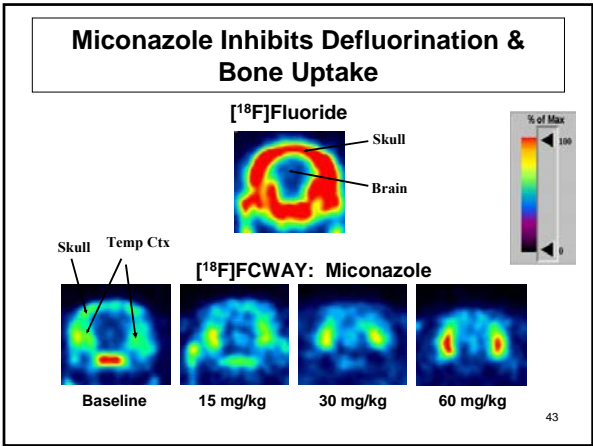
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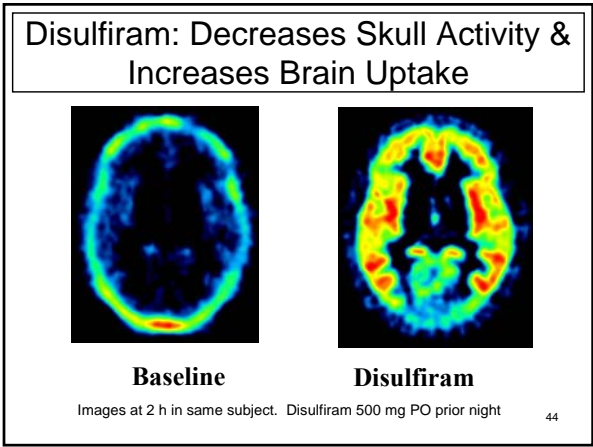
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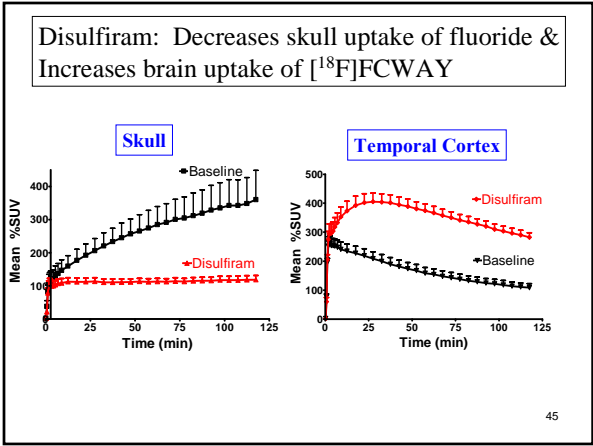
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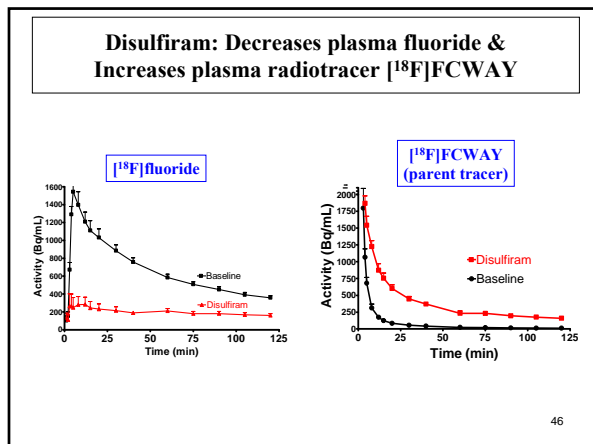
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### Summary of Talk

1. PET has high sensitivity and specificity
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### FDA Critical Path Initiative

- Approvals for new drugs declining
- R&D funding by industry and NIH is increasing
- Problem: tools are inadequate for efficient evaluation of new drugs in the “critical path” of development
- Still using old tools like liver enzymes and hematocrit to evaluate safety and efficacy
- Need new **Product Development Toolkit**

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## CRITICAL PATH to New Medical Products FDA, March 2004

“There is currently an urgent need for additional **public-private collaborative work** on applying technologies such as ... new imaging technologies.

Opportunity: **Imaging technologies**, such as molecular imaging tools in neuropsychiatric diseases or as measures of drug absorption and distribution, may provide powerful insights into the distribution, binding, and other biological effects of pharmaceuticals.”

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### Self-Assessment Quiz:

#### True or False?

- Positron emission tomography (PET) studies involve the injection of a radioactively labeled drug that emits a particle called a positron.
- PET shows the location of radioactivity in a cross section (or tomograph) of the body.
- PET can be used to quantify the density of specific proteins in the body.
- Compartmental modeling of PET data typically uses measurements over time of 1) PET images of the target tissue and 2) concentrations of unchanged parent radioligand in plasma.

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